Ultrafiltration Profiling and Outcomes Among Individuals on Maintenance Hemodialysis

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Ultrafiltration profiling and cardiovascular risk among individuals on maintenance hemodialysis

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LIST OF ABBREVIATIONS

IRB	Institutional Review Board
HD	hemodialysis
UF	ultrafiltration
BP	blood pressure
TTE	transthoracic echocardiography
GLS	global longitudinal strain
EF	ejection fraction
BP	blood pressure
PI	principal investigator
AE	adverse event
SAE	serious adverse event
UP	unanticipated problem

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of the Scientific Review Committee approval, and the conditions of the IRB approval. Additionally, the trial will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIH/ NIDDK terms of the award. The PI will assure that no deviation from, or changes to the protocol will take place without documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above requirements.

PI: Jennifer E. Flythe, MD, MPH

Signature: 

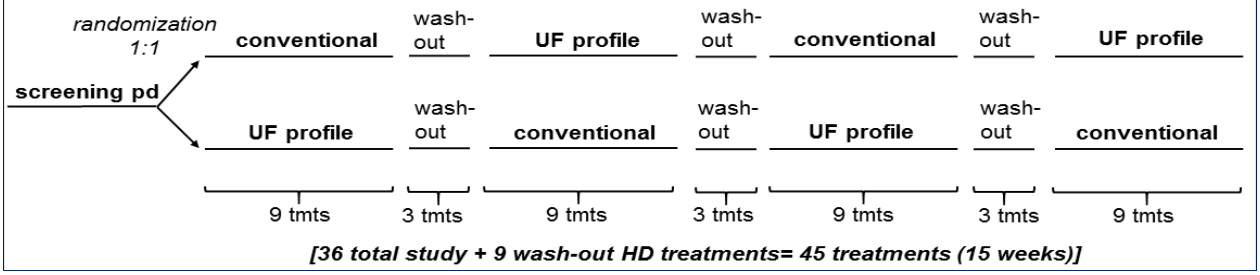
Date: 4/04/2018

PROTOCOL SUMMARY

Title:	Ultrafiltration (UF) profiling and cardiovascular risk among individuals on maintenance hemodialysis
Précis:	More rapid fluid removal (i.e. higher UF rate) is associated with adverse cardiovascular outcomes among maintenance hemodialysis (HD) patients. UF profiling may reduce UF-related cardiovascular complications. We will conduct a 4-period cross-over trial with 30 participants in which participants are alternated between UF profiling and standard HD therapy and key cardiovascular and patient-reported outcomes are assessed.
Objectives:	To investigate the comparative effect of UF profiling during HD and non-profiled conventional HD on select cardiovascular and patient-reported outcomes
Primary Endpoints	1) intradialytic hypotension, 2) troponin T change, 3) TTE-measured global longitudinal strain change
Population:	Adult individuals on maintenance HD for ≥3 months who have mean UF rates >10 mL/h/kg in the screening period who receive HD at a UNC-associated dialysis clinic (Carolina Dialysis Carrboro, Siler City, Pittsboro, Mebane, or Sanford)
Phase:	Phase 2
Number of Sites enrolling participants:	5 (all sites are UNC-based: Carolina Dialysis Carrboro and Siler City)
Description of Study Experimental Intervention:	Linear UF profiling is an HD technique in which the UF rate (fluid removal rate) is linearly decreased over the course of HD (starting UF rate= 1.33x the rate that would be needed at a constant UF rate to achieve the desired post-dialysis weight). The practice maximizes fluid removal during periods of greatest hydration and plasma oncotic pressure.
Study Duration:	15 months
Participant Duration:	4 months (+ 6 week screening period)

SCHEMATIC OF STUDY DESIGN

Figure 4. Cross-over study design.



[36 total study + 9 wash-out HD treatments= 45 treatments (15 weeks)]

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

United States HD patients have unacceptably poor outcomes with mortality rates greater than eight-fold those of individuals without kidney failure and symptom burdens on-par with those of cancer patients. Many difficult to modify factors such as co-morbid disease, chronic inflammation and poor nutrition contribute to the high morbidity and mortality experienced by HD patients. However, HD treatment factors also affect outcomes. Modifications of the HD procedure itself may represent feasible strategies to improve clinical outcomes. The rate of fluid removal during HD (UF rate) is a critical contributor to cardiovascular complications in HD patients. Higher UF rates are linked to greater morbidity and mortality. The mechanism likely relates to BP perturbations, myocardial ischemia, systemic inflammation, and other end-organ ischemic damage. In cases where fluid removal outpaces vascular refill rates, UF induces both subclinical end-organ hypoperfusion and frank hypotension. Hypoperfusion leads to regional myocardial hypoxia as evidenced by “stunning” on TTE and troponin elevation.

Hemodialysis procedural strategies, such as UF profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest hydration and plasma oncotic pressure, may reduce UF-related cardiovascular complications and patient-reported symptoms. See section 2.2 for UF profiling rationale. The objective of this study is to investigate the comparative effect of UF profiling during HD and non-profiled conventional HD on select cardiovascular and patient-reported outcomes.

2.2 RATIONALE

UF profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest hydration and plasma oncotic pressure, is one treatment modification that may reduce UF-related harm without necessitating reduction in interdialytic fluid intake or longer HD treatments. While UF profiling has been available for decades, it has not been adequately studied independently of sodium profiling. Sodium profiling uses a higher dialysate sodium concentration to increase plasma osmolality. While sodium profiling (± UF profiling) often reduces hypotension, it disadvantageously sodium-loads the patient. The resultant positive sodium balance leads to increased thirst, weight gain, and interdialytic hypertension. Sodium profiling has been dismissed as a viable treatment option due to these disadvantageous side effects. Alternatively, UF profiling may reduce UF-related hemodynamic instability and associated cardiovascular consequences without altering sodium balance. Hypotensive episodes occur when UF rates exceed plasma refill rates. UF profiling allows for lower UF rates later in the HD treatment when plasma refill rates are the slowest and hemodynamic instability risk the highest. Thus, UF profiling has the potential to improve hemodynamic stability without untoward sodium gains.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The risks involved in this study are small. Patients will complete 2 study arms (2 phases of each): UF profiling and conventional dialysis. Both forms of dialysis are used in clinical practice and are considered standard of care. Other than the different fluid removal paradigms, patients will undergo routine dialysis as prescribed by their treating nephrologists. All HD carries a risk of low blood pressure, heart rhythm abnormality, electrolyte abnormality, and bleeding. Patients are exposed to these risks each time they undergo dialysis. Participation in this study will not increase these baseline risks. There are no known risks associated with UF profiling. All study monitoring is low risk and part of routine dialysis care. Blood draws for laboratory testing will be low volume and will not exceed a total of 20 mL/ patient. Blood draws will be performed by experienced dialysis nurses, and blood will be taken from the cannulated dialysis access (thus no additional cannulations will be necessary). The main risk associated with the blood tests is bruising or bleeding at the access.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no additional direct benefit to the subjects participating. The results of this study may potentially benefit to future patients and their peers on dialysis. If individual participants experience improvement in UF-related cardiovascular risk or symptoms with UF profiling, UF profiling could be incorporated into their individual clinical dialysis prescriptions.

3 OBJECTIVES AND PURPOSE

The objective of this study is to investigate the comparative effect of UF profiling during HD and non-profiled conventional HD on select cardiovascular and patient-reported outcomes.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

The study is a 4-period cross-over trial (see schematic of study design) in which participants are successively alternated between study arms across 4 periods with intervening washout periods, and treatment order is randomized. The study control arm is conventional HD: the patient's standard HD prescription (no UF profiling). The study experimental arm is conventional HD + linear UF profiling. Linear UF profiling will be specified as a linearly decreasing UF rate with a UF rate starting at 1.33 times the rate that would be needed at a constant UF rate to achieve the desired post-weight (Fresenius 2008K machine profile 2). After providing consent, patients will be randomly allocated to experimental or control treatment for period 1. Patients will undergo 9 treatments during each phase for a total of 18 conventional HD treatments and 18 UF profiled treatments. Patients will undergo 3 wash-out HD treatments between phases. The study will be double-blinded in that patients will not be informed of the treatment paradigm. Investigators, including those performing TTE interpretation, will be blinded to treatment paradigm. Ultrasonographers performing intra-HD TTEs will be blinded to treatment paradigm.

4.2.1 PRIMARY ENDPOINT

1) Intradialytic hypotension: measured on a per-treatment basis; defined as nadir systolic BP <90 mmHg

2) Troponin T change: measured at the 7th treatment of each phase; defined as pre-HD – post-HD troponin T (ng/mL) and percentage change (troponin T rise) ≥10%

3) Left ventricular global longitudinal strain (GLS) on TTE: measured at baseline and 30 minutes before HD end during 7th treatment in the first phase of each treatment type (once during conventional and once during UF profiled treatment); defined as % GLS change (intradialytic GLS – baseline GLS), see Appendix A for TTE protocol. A change ≥2.5% indicates a clinically important change in GLS.

4.2.2 SECONDARY ENDPOINTS

1) Systolic BP change: measured on a per-treatment basis; defined as pre-HD – nadir intra-HD systolic BP (mmHg)

2) Nadir systolic BP: measured on a per-treatment basis; defined as the minimum intradialytic systolic BP (mmHg)

3) Target weight achievement: measured on a per-treatment basis: defined as post-HD weight within 1 kg of prescribed target weight.

4) Weight difference: measured on a per-treatment basis; defined as target weight – post-HD weight (kg)

5) Patient acceptance: measured after treatment 9 of each phase; response to the following question, "If recommended by your physician, would you be willing to adopt the HD prescription you have received during the last 9 treatments?"

6) TTE ejection fraction (EF): measured 30 minutes before HD end during 7th treatment in the first phase of each treatment type (once during conventional and once during UF profiled treatment); defined as % EF change (baseline – intradialytic EF), see Appendix A for TTE protocol

7) Patient-reported symptoms: measured after the 1st HD treatment each week; see Appendix B for data collection form.

4.2.3 EXPLORATORY ENDPOINTS

1) Early diastolic myocardial velocity (Em): measured 30 minutes before HD end during 7th treatment in the first phase of each treatment type (once during conventional and once during UF profiled treatment); calculated as the average of early diastolic velocities recorded at the medial and lateral mitral annulus, see Appendix A for TTE protocol

2) Tricuspid annulus systolic excursion velocity (S_t): measured 30 minutes before HD end during 7th treatment in the first phase of each treatment type (once during conventional and once during UF profiled treatment); measured as the distance of tricuspid annular movement between end-diastole to end-systole (cm), see Appendix A for TTE protocol

3) Blood volume monitor slope (by hour): measured during the 1st (last) HD treatment of each week, hour-by-hour basis; defined as change in blood volume (%) on an hourly basis

4) Blood volume monitor slope (by treatment): measured during the 1st (last) HD treatment of each week, from start to end of HD treatment; defined as change in blood volume (%) over the entire HD treatment

5) Plasma refill: measured 10 minutes before HD end during 7th treatment of each phase; defined as the percentage increase in hematocrit

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

- UF rate >10 mL/h/kg in >30% of treatments in a 4-week screening period (require ≥6 outpatient treatments in this period)
- Age 18-85 years
- Ability to converse comfortably in English or Spanish
- Receipt of in-center maintenance HD at Carolina Dialysis Carrboro, Siler City, Pittsboro, Mebane, or Sanford clinics
- ≥90 days on HD
- Free of bloodstream infection during 4-week screening period
- Willingness to undergo all study testing
- Evidence of a signed and dated informed consent document

5.2 PARTICIPANT EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria will not be eligible for randomization.

- Systolic BP unable to be measured by arm cuff
- >1 hospitalization during 4-week screening period
- Unstable angina per treating nephrologist

- End-stage cirrhosis per treating nephrologist
- New York Heart Association class IV heart failure per treating nephrologist
- Pregnant
- Dialysis treatment schedule increases to more than 4 times per week
- Incarcerated
- Anticipated kidney transplant within 6 months per treating nephrologist
- Non-adherence to HD prescription (>2 unexplained absences during 4-week screening period)
- Sodium profiling or UF profiling in standing HD prescription
- Decisionally challenged, unable to provide informed consent

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment goal is 36 participants (to account for drop-out) with study completion goal of 30 participants. The PI, a nephrologist, will identify eligible subjects from participating dialysis clinic (Carolina Dialysis Carrboro, Siler City) patient rosters and offer opportunity to participate in the study. If the patient does desire to participate in the research study, informed consent will be obtained by the PI or research staff. A study information sheet will be made available in the clinic for patients who desire additional information about the study. Participants will receive $20 for their time spent participating in the baseline TTE procedure because it is the only TTE performed outside of participants' regular dialysis treatment time. Participants will be compensated $45 for each 9 week treatment period and $20 for the baseline period TTE ($200 for full study completion).

Participants may miss study treatments. Missed study treatments will be considered "missed" and will not be made-up. For example, if a patient misses treatment #9 from arm 1, the patient will start wash-out treatments at the next treatment and will have missing data for treatment #9. The permeated design of the study arms (alternating conventional, UF profile, conventional, UF profile) was selected to maximize opportunities for data collection under each treatment paradigm. If participants are lost to follow-up (death, withdrawn consent, move to a new dialysis center), additional participants will be recruited until a study size of 30 participants is reached.

Based on the composition of the patient populations at the participating UNC sites, the expected sex breakdown is 50% male and 50% female and the expected enrollment of Hispanic or Latino participants is 10%. No exclusion by sex or by ethnic/ racial background will be made. There are no expected differences in the response to UF profiling across sex or racial/ ethnic groups. Children (individuals < 18 years) and vulnerable participants are not included in the study.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

- Active (voluntary) withdrawal of consent by the study participant
- Transfer of care to a non-participating dialysis clinic
- An investigator may terminate participation in the study if:
    - Non-adherence to study data collection procedures (refusal of TTE, blood draw or symptom monitoring)
    - Violation of the inclusion/ exclusion criteria determined after the fact
    - Any clinical AE, laboratory abnormality or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

While participants will be encouraged to complete the study, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any participant withdraws from the study prematurely. This information will be recorded. Withdrawn subjects will be replaced, until 30 participants complete the study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

If the investigators becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, the clinical study may be terminated after appropriate consultation between the involved parties. Conditions that may warrant termination of the clinical study include, but are not limited to: the discovery of an unexpected, relvant or unacceptable risk to the participants enrolled in the clinical study or failure to enroll participants at the required rate.

6 STUDY AGENT/ INTERVENTION

6.1 STUDY INTERVENTION AND CONTROL DESCRIPTION

6.1.1 DESCRIPTION

Intervention (UF profile during HD): The study intervention arm is linear UF profiling (linearly decreasing UF rate with a UF rate starting at 1.33 times the rate that would be needed at a constant UF rate to achieve the desired post-weight; pre-programmed “profile 2” on a Fresenius 2008K machine, the machine used in all participating clinics).

Routine care/ control (conventional HD): The study control arm is conventional HD (the patient’s standard HD prescription without UF profiling).

6.1.2 DURATION OF THERAPY

Patients will undergo 9 treatments during each phase for a total of 18 conventional HD treatments and 18 UF profiled treatments. Patients will undergo 3 wash-out HD treatments between phases. There will be a total of 45 study treatments (36 study treatments and 9 washout treatments). The baseline study visit will involve a history and physical and baseline transthoracic echocardiography study. The entire study duration for each individual is 16 weeks (15 treatments and 1 baseline study visit).

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

N/A

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

UF profiled HD treatments (intervention): The study treatments will be administered at routine, scheduled outpatient thrice-weekly HD clinic visits. Dialysis clinic nursing staff will select UF profile 2 on the dialysis machine at the start of each UF profiled treatment. Clinic nursing staff have experience using UF profiling as it is a standard HD machine setting. Dialysate composition and HD medications will be per baseline prescription determined by the treating nephrologist. Total UF volume and target weight will be determined by the treating nephrologist.

Medical history: At baseline, the participant’s medical history will be taken from the electronic medical record and confirmed verbally with the patient. The medical history will include a review of co-morbid conditions, medications

and performance of a physical examination (Vital signs- BP, heart rate, respiratory rate, weight, height; systems- cardiovascular, pulmonary, neurological)

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Standard HD treatments without UF profiling (control): Fresenius 2008K HD machines, a dialysate temperature of 37°C, and patients' standard blood and dialysate flows will be used. No sodium profiling will be used. Dialysate composition and HD medications will be per baseline prescription determined by the treating nephrologist. Total UF volume and target weight will be determined by the treating nephrologist.

Standard-of-care BP measurement: BPs will be machine-measured with an upper extremity cuff in the seated position pre- and post-dialysis and every 20 minutes during every dialysis treatment.

Standard-of-care weight measurement: Per routine practice, target weight will be estimated by the treating nephrologist. Pre- and post-dialysis weights will be measured before and after each treatment in the standing position.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Troponin T (blood sample): Blood samples for Troponin T measurement will be collected via the vascular access by dialysis clinic staff. Troponin T will be collected before and after the 7th HD treatment of each phase for the calculation of troponin T change (2 troponin T changes during UF profiled HD and 2 during control HD). Troponin T is the only laboratory test to be performed as part of the study.

Standard-of-care laboratory measurements: Study start will be timed so that standard-of-care monthly lab testing (electrolytes, albumin, complete blood count, Kt/V, iron stores, bone-mineral tests) will be drawn within 6 weeks prior to study start (baseline). A 24-hour urine collection will be performed during baseline to measure residual kidney function (mL urine/day). These standard-of-care laboratory measurements will be performed as part of routine clinical care and are not study-specific.

7.2.2 OTHER ASSAYS OR PROCEDURES

TTE: Patients will undergo intradialytic TTE at baseline (within 6 weeks prior to study start) and 30 minutes prior to HD end ("peak stress") during treatment 7 of the first phase of each treatment type (once during conventional and once during UF profiled treatment) (1 TTE during UF profiled HD and 1 during control HD). Study TTEs will be performed by a trained sonographer with a Philips CX50 ultrasound system (Philips North America).

Blood volume monitoring: Blood volume monitoring will be performed continuously throughtout each study treatment via a Crit-line™ (standard-of-care non-invasive relative blood volume monitoring tool used as part of standard dialysis treatments).

Plasma refill test: Using the blood volume monitor, a plasma refill test will be performed 10 minutes before HD end during the 7th treatment of each phase. At the start of the treatment, UF time will be set 10 minutes less than treatment time. When the dialysis UF ends, study staff will document the hematocrit (%) from the blood volume monitor, and when the treatment ends, document the blood volume monitor hematocrit (%) again. Plasma refill tests are part of the blood volume monitoring protocols at the selected units and are familiar to staff.

Patient acceptance: At the end of the 9th study treatment of each phase, study staff will ask the participant the following question: "If recommended by your physician, would you be willing to adopt the HD prescription you have received during the last 9 treatments?"

Symptom assessment: At the conclusion of the 1st study treatment each week, study staff will ask patients to complete a symptom questionnaire (Appendix B).

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Blood samples for Troponin T measurement will be collected via the vascular access by HD staff. Samples will be transported (on the day they are drawn by study staff) on ice for aliquoting and storage at -80°C in UNC Kidney Center freezers. Baseline blood (electrolytes, albumin, complete blood count, Kt/V, iron stores, bone-mineral tests) and 24-hour urine samples are being collected as part of routine care processes and will be processed per usual clinical procedures at an accredited laboratory.

7.2.4 SPECIMEN SHIPMENT

After aliquoting and transporting to UNC, Troponin T samples will be shipped to an accredited laboratory for testing per usual clinical procedures.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

The PI will communicate with potential participants to determine whether they fit the inclusion/exclusion criteria and would like to participate in the study. If patients are interested in participating, a signed HIPAA waiver will be obtained to allow the PI to review the individual's medical record and confirm eligibility status. The study baseline period will begin within 4 weeks of enrollment.

7.3.2 ENROLLMENT/BASELINE

Written informed consent will be obtained from study subjects prior to the implementation of any study procedures. The subject will receive a signed and dated informed consent form. The PI will verify inclusion/ exclusion criteria. A complete medical history, physical examination and baseline TTE will be taken at the time of enrollment (baseline).

7.3.3 FOLLOW-UP

All study visits will occur at the time of routinely scheduled dialysis treatments at the patient's usual outpatient dialysis clinic. Monitoring and recording of BP and weights will be performed at every treatment. See "7.3.7 Schedule of Events Table" for planned frequency of additional monitoring and testing.

7.3.4 FINAL STUDY VISIT

N/A (the final study visit is no different than the follow-up visits).

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Baseline (6 week prior to study start)	Every study HD treatment	Before and after 7th HD treatment of each phase	During 7th HD treatment of each phase (twice per treatment type)	During 7th HD treatment in the first phase of each treatment type (once per treatment type)	After 9th HD treatment of each phase	After 1st HD treatment of each week (3x/phase)		
Baseline laboratory testing	X								
Baseline history and physical	X								
Pregnancy status inquiry	X								
BP monitoring	X	X							
Weight monitoring	X	X							
Blood volume monitoring	X						X		
Troponin T laboratory testing			X						
TTE	X				X				
Plasma refill test	X			X					
Patient acceptance assessment						X			
Symptoms assessment							X		

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

N/A

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

There will be no change to a patient's usual medications or dialysis treatments (other than UF profiling during UF profiled arms).

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Any hemodynamic instability experienced during study HD will be managed per routine protocols with standard interventions (e.g. saline administration, reduction in UF rate or blood flow).

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will have access to UF profiling during HD treatments at study closure if deemed appropriate by their treating nephrologists.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

All HD carries a risk of low BP, heart rhythm abnormality, electrolyte abnormality, and bleeding. Patients are exposed to these risks each time they undergo dialysis. Participation in this study will not increase these baseline risks. There are no known risks associated with UF profiling. All study monitoring is low risk and part of routine dialysis care. The study involves one non-standard blood draw (Troponin T) which will be taken from the vascular access and not require a separate "stick" and one non-standard monitoring test (TTE) which is non-invasive and free of discomfort or complications.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of the experimental treatment) in a patient or clinical investigation subject administered an experimental treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal vital sign finding) or symptom temporally associated with the use of the experimental treatment, whether or not related to the experimental treatment. Each AE will be graded on a mild-moderate-severe scale. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE.

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the experimental treatment is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the experimental treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by an experimental treatment. Each SAR will be graded on a mild-moderate-severe scale.

Causality assessment to an experimental treatment is a medical judgment made in consideration of the following factors: temporal relationship of the AE to the experimental treatment exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug or treatment exposures, normal clinical course of the condition under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- One or more occurrences of an event not commonly associated with experimental treatment exposure, but otherwise uncommon in the population (e.g. severe symptomatic hypotension); often more than one occurrence from one or multiple studies would be needed before the study oversight physician could determine that there is *reasonable possibility* that the experimental treatment caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the experimental treatment group than in the control group.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is considered serious (SAE) if, in the view of the study oversight physician, it results in any of the following outcomes:

- Death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experimental treatment experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An AE or SAE is considered unexpected if the specificity or severity of it is not consistent with the applicable experimental treatment information (e.g., dialysis machine approved product brochure).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Each AE will be graded on a mild-moderate-severe scale by the monitor as described above.

8.2.2 RELATIONSHIP TO STUDY EXPERIMENTAL TREATMENT

An AE or SAE will be considered potentially related to the study experimental treatment if it occurs during an HD treatment in which the experimental treatment (UF profiling) is being administered.

8.2.3 EXPECTEDNESS

There are no known expected AE or SAEs associated with the study experimental treatment (UF profiling). An AE will be considered unexpected if the nature, severity or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits or upon review by a study monitor. All AEs not meeting the criteria for SAEs will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clincian's assessment of severity, relationship to the study intervention, and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermitten require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Events meeting the criteria for an AE will be documented within 24 hours of occurrence. A summary of AEs, including evaluation of the AEs by the monitor will be submitted to the IRB at the time of the progress report.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Events meeting the criteria for an SAE will be documented within 24 hours of occurrence. The IRB will be notified of all SAEs that qualify as an unanticipated problem as per the UNC IRB policies within 7 days of the investigator being notified of the event.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Events meeting the criteria for an unanticipated problem will be documented within 24 hours of occurrence.

8.4.4 EVENTS OF SPECIAL INTEREST

N/A

8.4.5 REPORTING OF PREGNANCY

Pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is enrolled will result in study cessation for the pregnant subject. The female subject will be referred to an obstetrician-gynecologist. Pregnant dialysis patients require more intensive dialysis therapy and are not appropriate for ongoing study participation. The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

8.5 STUDY HALTING RULES

If there is an SAE suspected to be related to the study intervention, UF profiling, the study will be put on hold and re-evaluated as this would not be an expected event.

8.6 SAFETY OVERSIGHT

The PI will provide continuous, close monitoring of the study. Trained dialysis nurses and technicians will administer the HD treatments per routine care and will have 24-hour telephone and pager access to the PI. A licensed dialysis physician will also be immediately available to the HD units during study HD treatments. Participating patients will be given the PI's direct contact information. If there is concern for an AE or SAE, an attending nephrologist (other than the PI who will be blinded to study treatment arm) will assess and record any AE or SAE in detail including the time of onset, description, severity, time course, duration, and outcome, relationship of the AE/SAE to study arm, and any action(s) taken. Two additional attending nephrologists will review study-associated morbidities no more than two days after they occur in order to determine whether further safety guards should be instituted and whether the benefit of the study continues to outweigh potential risks. The PI will report all adverse events to the IRB and funding institute and center on the day of occurrence. The PI will discuss all morbidities with project co-investigators. The PI will personally review all study results and notify

subjects of any abnormal results, including those present at baseline unrelated to the treatment to ensure subjects are able to seek appropriate medical care.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s) and with GCP. The PI and research Study Coordinator will conduct on-site monitoring (at least once per study phase) and centralized monitoring (every study treatment) for all study participants at all study sites to verify protocol adherence/ study conduct, data collection, and safety.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This is an investigator-initiated 4-period cross-over trial. Statistical and analytical plans were developed in consultation with statistical experts. See below for details.

10.2 STATISTICAL HYPOTHESES

We hypothesize that patients will have comparatively less hypotension, troponin change and left ventricular global longitudinal strain change with UF profiling vs. conventional HD.

10.3 ANALYSIS DATASETS

Analytical datasets will be compiled from collected clinical data. Datasets will include an intention-to-treat analysis dataset and a modified intention-to-treat analysis dataset. Data analysis will be performed with STATA 12.2MP. Datasets will be de-identified and maintained on a secure UNC Department of Medicine Server that is accessed via a password-protected UNC computer with anti-virus and UNC firewall protection.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

By cross-over design, each participant will act as his or her own control, permitting between and within group comparisons. Analyses will be performed on an intention-to-treat and modified intention-to-treat basis, separately. Comparisons of values between HD treatments will be performed by repeated-measures analysis of variance (ANOVA; or non-parametric methods depending on data type) for continuous outcomes and generalized estimating equations for categorical outcomes. Analagous analyses will be performed in both the intention-to-treat and modified intention-to-treat datasets. All statistical estimates will be tablulated along with their corresponding 95% confidence intervals. All reported P values will be 2-sided; <0.05 representing significance. All hypothesis tests that are observed to be statistically non-significant will be interpreted as such and reported as being inconclusive. However, as this is a small, pilot study, the magnitude of estimates and the corresponding confidence intervals will be considered in the results interpretation.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Comparisons of values for the binary primary endpoints of hypotension and troponin T rise ≥10% between HD treatments will be performed using generalized estimating equations. Comparisons of values for the continuous

primary endpoint of global longitudinal strain change will be performed using ANOVA or non-parametric methods depending on data type.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Comparisons of values for the binary secondary endpoints of target weight achievement, patient acceptance, and symptom occurrence between HD treatments will be performed using generalized estimating equations. Comparisons of values for the continuous secondary endpoints of pre-HD to nadir intradialytic HD systolic BP change, intradialytic nadir systolic BP change, target and post-HD weight difference, and TTE ejection fraction change will be performed using ANOVA or non-parametric methods depending on data type.

10.4.4 SAFETY ANALYSES

See "8.6. Safety Oversight." The primary safety endpoint that will be monitored is BP but all AEs and SAEs will be evaluated for safety concerns.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Adherence and retention will be analyzed on a weekly basis by the PI and study coordinator throughout the course of the study.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline patient characteristics will be reported as counts and proportions for categorical variables, and as means and standard deviations or medians and inter-quartile ranges for continuous variables.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

See "8.6. Safety Oversight." This will be performed on an ongoing basis throughout the course of the study by 2 nephrologists not associated with the study. There will be 2 formal interim statistical analyses of nadir systolic BP and pre- to post-dialysis BP change across the trial arms: 1) after 10 participants have completed 2 phases of the study (1 conventional and 1 UF profiling phase) and 2) after 20 participants have completed 2 phases of the study (1 conventional and 1 UF profiling phase). Statistical rules will not be used to halt study enrollment.

10.4.7.2 EFFICACY REVIEW

Efficacy review will be performed at the completion of the study or at the time of termination if the study is terminated early.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

N/A

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

There are 3 primary outcomes. Analyses will be performed with and without correction for multiple testing. The Bonferoni correction will be used to adjust confidence intervals to decrease type 1 error when adjusting for multiple testing.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual data will not be collected and stored by individual measure and timepoint, but individual data will not be publicly reported in this manner (reported only in aggregate).

10.4.11 EXPLORATORY ANALYSES

Comparisons of values for the continuous exploratory endpoints of early diastolic myocardial velocity change, tricuspid annulus systolic excursion velocity change, blood volume monitor slope change and plasma refill change will be performed using ANOVA or non-parametric methods depending on data type.

10.5 SAMPLE SIZE

This cross-over study is designed as a pilot study to test for efficacy signals. However, with its cross-over design in which each participant acts as his or her own control, we are powered to detect clinically and statistically significant differences across arms within patients. With a sample size of 30, we have 80% power to detect a 5.9 mmHg difference in nadir SBP (S.D. 8), a ≥0.07 ng/mL troponin T difference (S.D. 0.1), a 2.2% strain difference (S.D. 3), and 4% ejection fraction difference (S.D. 5); all clinically meaningful differences. We have 80% power to detect a 31% absolute difference in the binary endpoint of Troponin T change >0.1 ng/mL (event rate=20%).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Randomization assignments will be generated using computer-generated random numbers. Assignments will be sealed in envelopes prior to study start. After patients consent to study participation, sealed study arm assignments will be randomly allocated to experimental or control treatment for period 1. Sequence assignments will be sealed in envelopes prior to study start and opened in a predetermined order at the start of each study period. The study will be double-blinded in that patients will not be informed of the treatment paradigm. Investigators, including those performing TTE interpretation, will be blinded to treatment paradigm. Ultrasonographers performing intra-HD TTEs will be blinded to treatment paradigm.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

At study close-out for each participant, we will assess blinding with qualitative questions regarding the participant's perception of the order of administered treatments.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

The PI may only break the study code in an emergency (occurrence of an SAE where it is necessary for the PI or treating physician to know which treatment the patient is receiving before the participant can be treated) or at the end of the study. Breaking the study blinding/ participant code will be reported to the IRB.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH IC-sponsored study, each site will permit authorized representatives of the NIH IC and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity. Study staff will have access to study records.

Data (blood pressures, weights, dialysis treatment data) will be extracted from electronic medical records and stored in password-protected Excel flowsheets housed on a secure Department of Medicine server. Blood

volume monitor, treatment preference, and symptoms will be recorded on study data collection forms. TTE data will be downloaded from the TTE machine to secure Deparment of Medicine Servers, per standard protocols. All electronic information will be stored on a password-protected UNC server (with secure, password and firewall-protected Department of Medicine server back-up) and accessed via a UNC password-protected computer and will be identifiably by study identification number only. Information linking the study identification number to the patient will be kept in a separate, password-protected database on the server. Study charts will be maintained in a locked room of the dialysis clinic. Study charts will be identified by study IDs. Signed consent forms will be kept in a locked filing cabinet in the PI's locked office. Initial paper records of study HD treatment data, patient preferences and symptoms will be stored in the study chart and, after study completion, will be transferred to a locked filing cabinet in the locked office of the PI. Paper records will be destroyed (shredded and disposed in locked, shred bins) after verification of electronic data entry. Only the PI and research assistant will have access to patient information with patient identifiers.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Following written SOPs, the monitors will verify that the clinical trial is conducted and data generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. The investigational site will provide direct access to all trial-related sites, sources data/ documents,a nd reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

The PI will be responsible for quality assurance and quality control and will provide oversight of all research team members to assure adherence to the protocol. Except for in an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigators will adhere to NIH Human Research Protections Program policies and procedures.

13.2 INSTITUTIONAL REVIEW BOARD

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The protocol, informed consent, recruitment materials and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented. The investigators will adhere to NIH Human Research Protections Program policies and procedures.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

An IRB-approved consent form and IRB-approved study informational page will be provided to potential participants.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

In obtaining and documenting informed consent, the investigators will comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) Good Laboratory Practice (GLP) and to ethical principles that have their origin in the Declaration of Helsinki. The PI will approach eligible patients and offer then the opportunity to participate in the study. If the patient does desire to participate in the research study, informed consent will be obtained by the PI. The purpose of the informed consent procedure is to assist the patient in understanding the nature and purpose of the study and the risks and benefits of the study, to offer answers to questions about any details of the study, and to obtain the patient's signature on the IRB-approved consent form. All patients will be reminded that participation in the study is voluntary and that their medical care will not be affected if they choose not to participate. The patients will be informed that they will be free to terminate participation at any time during the study. The rights and welfare of participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

We are recruiting English-speaking and Spanish-speaking individuals for this study. Each participating dialysis clinic has in-clinic non-English interpretation coverage by a professional interpreter. The interpreter will interpret for Spanish-speaking patients while the Principal Investigator or other study staff consent patients for the study. If Spanish-speaking participants have questions outside of study visit times, the interpreter will provide language interpretation over the phone. In addition, one of our Research Assistants is Spanish-speaking.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Study procedures and data collection will be performed after informed consent is obtained via patient signature on the IRB-approved consent form. All electronic information will be stored on a password-protected UNC computer (with secure, password and firewall-protected Department of Medicine server back-up) in the locked office of the study Principal Investigator and will be identifiably by study identification number only. Information linking the study identification number to the patient will be kept in a separate, password-protected database on the computer. Signed consent forms will be kept in a locked filing cabinet in the Principal Investigator's locked office. Initial paper records of study HD treatment data will be stored in a locked filing cabinet in the locked office of the Principal Investigator. Paper records will be destroyed (shredded and disposed in locked, shred bins) after verification of electronic data entry. Only the Principal Investigator and research assistant will have access to patient information with patient identifiers. No documents containing patient information with patient identifiers will be downloaded off of the secure Department of Medicine server onto personal computers.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

One vial of stored blood will be maintained in UNC Kidney Center freezers (5th floor Burnett-Womack) until 12 months after study completion. Access to stored samples will be limited to study staff. Samples and data will be stored using codes assigned by the investigators. Data will be kept on password-protected secure Department of Medicine servers. Only study staff will have access to the samples and data. Study participants who request destruction of the sample prior to the 12 months after study completion date will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5 FUTURE USE OF STORED SPECIMENS

With the participant's approval and as approved by the IRB, de-identified biological samples will be stored in the UNC Kidney Center freezers (5th floor Burnett-Womack). After the study is completed, the de-identified, archived blood sample will be maintained for 12 months under the supervision of the PI, Dr. Flythe. There will be no transfer of the specimens for use outside of the study. Potential additional laboratory testing (e.g. B-type natriuretic

peptide) relevant to this study may be performed. No genetic testing will be performed. The potential for additional laboratory testing on stored specimens will be listed in the IRB-approved consent form.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future use. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Research material for this study will consist of baseline patient data including demographics, co-morbidities, biochemical data, and HD treatment data (dialysate, dialysis time, target weight, UF volume, and medications) collected via patient interview and electronic medical record review. During the study HD treatments, patient vital signs (including blood pressures and weights) will be collected. Patient data will be identified with a study identification number. Patient-signed study informed consent forms will contain patient names and signatures. These consent forms will be stored separately from other study data in a locked filing cabinet in the Principal Investigator's locked office. Only the Principal Investigator and research assistant will have access to consent forms.

The collected study data will not contain participants' names, medical record numbers, social security numbers, or contact information (address, telephone number), such that these data cannot be linked back to the source patients. Data collected about patients will be labeled with a study identification number. A database linking patient names and study identification numbers will be maintained separate from the study data. This database will be password-protected and will be maintained on a password-protected UNC Department of Medicine server that is accessed via a UNC password-protected computer with anti-virus and UNC firewall protection. The study statistician (to-be-named) will have access to the de-identified electronic data.

The PI will be the primary responsible party for the oversight and management of the study data. The study research coordinator will assist with data management.

14.2 STUDY RECORDS RETENTION

Study documentation includes all case report forms, data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases (as applicable to this study), study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.3 PROTOCOL DEVIATIONS

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s)
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations**:** UNC personnel will record the deviation in a Case Report Form and report to IRB or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations**:** Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems**:** Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscrjipts to the digital archive PubMed Central upon acceptance for publication. The study will be registered at clinicaltrials.gov, sponsored by the National Library of Medicine.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

Jennifer E. Flythe, MD, MPH (Principal Investigator); UNC School of Medicine; 919-445-2656; jflythe@med.unc.edu

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Julia Narendra, MPH (Study Coordinator); UNC School of Medicine; 919-445-2686; julia3@email.unc.edu

The steering committee will review the progress of the study together every 4 months.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. All study personnel will adhere to the the conflict of interest policy set forth by the University of North Carolina at Chapel Hill.

17 LITERATURE REFERENCES

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Appendix A: Transthoracic Echocardiography (TTE) Protocol

The imaging protocol described below is designed primarily to assess intradialytic left ventricular systolic function by measuring myocardial strain by speckle tracking imaging. Left ventricular ejection fraction by two-dimensional echocardiography, right ventricular function, and left ventricular diastolic function will also be evaluated.

Image acquisition

Data storage and labeling

- Studies should be labeled with the participant's identification number, study number, and date of the study.
- Each echocardiographic study will be stored on the hard drive of the ultrasound machine and copied in native and DICOM formats onto a compact disc for subsequent off-line analysis.

General procedure

- Imaging will be performed during quiet respiration with the subject in the left lateral decubitus position. All tracings will be recorded with a simultaneous electrocardiogram.
- Harmonic imaging will be utilized, and transducer orientation and gain settings will be carefully adjusted to optimize imaging of the epicardial and endocardial surfaces of the ventricles.
- Tissue Doppler imaging will be performed at a 25 mm/second sweep speed.\
- 2D images will be stored digitally in loops consisting of 3 beats. Tissue Doppler tracings containing 3 consecutive frames will be stored for each spectral display.

Imaging protocol

As described in detail below, images should be recorded in the following sequence:

Apical 4-chamber view
Apical 2-chamber view
Apical long axis view

Apical 4-chamber view: A standard apical 4-chamber view of the heart will be obtained with the ultrasound beam oriented to obtain the maximal dimensions of the left and right ventricles. Tissue Doppler imaging of mitral and tricuspid annular motion will then be performed. Initially the lateral mitral annulus will be interrogated, placing the sample volume within the lateral wall of the left ventricle, adjacent to the mitral annulus. The transducer will be oriented so that the ventricular wall is parallel to the cursor, and 5 consecutive beats showing peak Sm, Em, and Am velocities will be recorded. The septal mitral annulus will be interrogated in similar fashion. The anterior tricuspid annulus will then be interrogated by placing the sample volume within the right ventricular free wall, adjacent to the tricuspid annulus.

Apical 2-chamber view: Standard 2-chamber images of the left ventricle, with the transducer angled to maximize the left ventricular long axis dimension, will be acquired.

Apical long axis view: Standard apical long axis images of the left ventricle, with the transducer angled to maximize the left ventricular long axis dimension, will be acquired.

Image analysis

Global longitudinal strain: Left ventricular function will be quantified by 2-dimensional speckle tracking echocardiograpy-derived global longitudinal strain. The apical 4-chamber, 2-chamber, and long axis views will be optimized and analysed offline using a dedicated computer workstation equipped with Philips QLab software. Aortic valve closure time will be defined on the apical long-axis view. After the mitral annulus and apical left ventricular endocardium are identified, a region of interest will be automatically defined and edited as necessary. Global longitudinal strain will be calculated as the average of all 3 apical views.

Left ventricular ejection fraction: The areas of the left ventricle at end-diastole and at end-systole will be quantified by tracing the endocardial border (excluding trabeculations and papillary muscles) in the apical 2-chamber and 4-chamber views. Left ventricular volumes at end-diastole and at end-systole will be computed using the biapical Simpson's rule. Ejection fraction will be calculated as percentage change in left ventricular volumes.

Early diastolic myocardial velocity (E_m): Left ventricular diastolic function will be quantified as the early diastolic myocardial velocity (E_m) calculated as the average of early diastolic velocities recorded at the medial and lateral mitral annulus.

Tricuspid annulus systolic excursion velocity (S_t): Right ventricular systolic function will be quantified as the peak systolic excursion velocity (S_t) of the anterior tricuspid annulus.

PATIENT-REPORTED SYMPTOMS DURING DIALYSIS

INSTRUCTIONS

Please respond to each statement by marking one box per row.

We are interested in the symptoms you had DURING your dialysis treatments LAST WEEK. Respond ONLY based on the dialysis treatments last week.

During your dialysis treatments last week, did you have **CRAMPING?**	No cramping ☐	Mild cramping ☐	Moderate cramping ☐	Severe cramping ☐	Very severe cramping ☐
During your dialysis treatments last week, did you have **NAUSEA or UPSET STOMACH?**	No nausea ☐	Mild nausea ☐	Moderate nausea ☐	Severe nausea ☐	Very severe nausea ☐
During your dialysis treatments last week, did you have **VOMITING or THROWING UP?**	No vomiting ☐	Mild vomiting ☐	Moderate vomiting ☐	Severe vomiting ☐	Very severe vomiting ☐

During your dialysis treatments last week, did you have **DIZZINESS or LIGHTHEADEDNESS?**	No dizziness ☐	Mild dizziness ☐	Moderate dizziness ☐	Severe dizziness ☐	Very severe dizziness ☐

During your dialysis treatments last week, did you have **RACING HEART or HEART PALPITATIONS?**	No racing heart ☐	Mild racing heart ☐	Moderate racing heart ☐	Severe racing heart ☐	Very severe racing heart ☐

During your dialysis treatments last week, did you have **CHEST PAIN?**	No chest pain ☐	Mild chest pain ☐	Moderate chest pain ☐	Severe chest pain ☐	Very severe chest pain ☐

During your dialysis treatments last week, did you have **SHORTNESS OF BREATH?**	No shortness of breath ☐	Mild shortness of breath ☐	Moderate shortness of breath ☐	Severe shortness of breath ☐	Very severe shortness of breath ☐

During your dialysis treatments last week, did you have **THIRST or DRY MOUTH?**	No thirst ☐	Mild thirst ☐	Moderate thirst ☐	Severe thirst ☐	Very severe thirst ☐

During your dialysis treatments last week, did you have **HEADACHE?**	No headache ☐	Mild headache ☐	Moderate headache ☐	Severe headache ☐	Very severe headache ☐

During your dialysis treatments last week, did you have **ITCHING?**	No itching ☐	Mild itching ☐	Moderate itching ☐	Severe itching ☐	Very severe itching ☐

During your dialysis treatments last week, did you have **RESTLESS LEGS or DIFFICULTY KEEPING LEGS STILL?**	No restless legs ☐	Mild restless legs ☐	Moderate restless legs ☐	Severe restless legs ☐	Very severe restless legs ☐

During your dialysis treatments last week, did you have **TINGLING or FEELING OF PINS AND NEEDLES?**	No tingling ☐	Mild tingling ☐	Moderate tingling ☐	Severe tingling ☐	Very severe tingling ☐

During your dialysis treatments last week, did you have **OTHER SYMPTOMS? (write-in)** _____	No _____ ☐	Mild _____ ☐	Moderate _____ ☐	Severe _____ ☐	Very severe _____ ☐

AFTER your dialysis treatments LAST WEEK, how long did it take for you to recover?

_____ hour(s)

Ultrafiltration (UF) profiling and outcomes among individuals on maintenance hemodialysis: statistical analysis plan

Primary Analysis

Depending on the type of various endpoints, we propose to perform the following tests to test the difference between UF profile and conventional treatment.

- `Binary Outcomes`
  - We will perform repeated measure logistic regression by regressing the binary outcome on the treatment indicator and test if the coefficient before the treatment indicator is significant. Each subject will have a random intercept. The model is given by

$$logit(outcome) \sim 1 + treatment + (1|ID)$$

- `Continuous Outcomes`
  - We will perform repeated measure linear regression by regressing the continuous outcome (percentage outcome will be log-transformed) on the treatment indicator and test if the coefficient before the treatment indicator is significant. Each subject will have a random intercept. The model is given by

$$outcome \sim 1 + treatment + (1|ID)$$

- `Categorical Outcomes`
  - We will perform repeated measure multinomial regression by regressing the categorical outcome on the treatment indicator and test if the coefficient before the treatment indicator is significant. Each subject will have a random intercept. The model is given by

$$multi - logit(outcome) \sim 1 + treatment + (1|ID)$$

Quality Check

For patients who dropped out during the study, normalize endpoints to the same scale as the other patients, depending on the type of endpoints.

Sensitivity Analyses

1. Exclude participants who dropped out from all analyses.
2. Exclude participants who had endpoint data drawn "off-schedule" (troponin T, symptoms, etc.) from individual endpoint analyses.
3. Exclude participants who had an abnormality with their troponin T blood draw from troponin T-related analyses.
4. Test for difference by order of randomization (UF profiling --> conventional --> UF profiling --> conventional) vs. (conventional --> UF profiling --> conventional --> UF profiling)
5. Test for difference by clinic (site 1 vs. site 2)